The Lister Institute of Preventive Medicine.

CHELSEA BRIDGE ROAD,
LONDON, S.W.1.

Telegrams : "Bacteriology, Knights, London."
Telephone : SLOANE 2181.

6th.April 1955.

Professor J.Lederberg,
Department of Genetics,
University of Wisconsin,
Madison,
Wis, U.S.A.

Dear Josh,

Many thanks for your letters of March 5 and 30. I am glad to hear that Wright has done so well.

I am sorry to find we still don't see eye to eye on interpretation. As far as I am concerned, my notion of two classes of non-replicating particles is, I feel, reasonably established by my "large pedigree" experiments, which otherwise seem inexplicable. Your new experiments appear to cast some doubt on the attribution of trails (on standard motility medium with SW 541) to the "gene-bearing" cell, since they suggest that a cell with a m.c.p only may initiate a trail (on diluted medium with SW 553). However, if you still consider the particulate nature and non-reproductive character as "amply settled" (your letter of Jan.26) then the SW 541 trails on standard medium cannot be attributed to m.c.p.-bearing cells, since count of colonies compared with maximum number of generations possible in period of incubation demands phenotypic lag in loss of motility of more than 1 generation. On my theory the probability of moving through medium is a function of numberof m.c.p, with a probability of zero (or near it) for mono-particulate cells inferred from absence of macro-branching; one would expect a priori, and your experiments on spontaneous "deeps" in SW 553 (and ours on the same phenomenon in SW 545 and other strains), indicate, I think, that the probability of not getting stuck is also a function of gelatin-agar concentration. On this interpretation the 2 trails on standard medium shown in your table would be nearly certainly trails produced by gene-bearers, and it would remain to decide what proportion, if any, of the trails which developed on softer medium only grew from cells with 1 or more m.c.p only. As you incubated 8 hours at 37°, a count of more than, say 30 colonies in a trail would disprove its origin from a m.c.p cell. A critical test of my interpretation of your data might be possible in the case of your platings of clones which you say on occasion give as many as 7 trails. On my interpretation no more than 1 of these grew from a gene-bearer, the rest should

therefore each contain fewer colonies than No. of generation times at 37°. (How many colonies (about) do you mean by "a well-developed trail", in this context ?). In a fluid medium a mono-particulate cell ought to produce a trail, though it might be marked by diffusion of non-motiles. So far, all your evidence seems to me compatible with the hypothesis; I shall of course be much disconcerted if you come up with something which disproves it, but on the whole I feel fairly confident (even willing to bet). Have you ever tried a macro-pedigree on 541 ? It may be that it is easier to re-isolate the E cell late in this strain. This is I agree the hard way, but perhaps more informative.

As to publication, for a joint preliminary account P.N.A.S. is agreeable to me, though I would have thought Nature just as suitable Why should papers in Nature be more discursive ? Or is this a mis-type for less? What will be more difficult will be to decide on content. We are, I take it, agreed on the mono-mcp. concept, and we have good evidence for its occurrence in 3 situations, viz. in abortive clones, in clone of sib of transformed cells and in clone produced by spont. motile in O strains like 545 and 553. Q. here is working on a probable 4th.type, viz. result of distribution out after transfer to environment in which mcp not formed. As we don't yet agree on what happens in abortive transduction I suppose the sib of transformed cell case may be clearest. If the preliminary paper is devoted mainly to the mono-mcp case, and hedges on "abortives", then I suppose it might be necessary to bring in the spont. motiles, in which case we should join Quadling as a co-author I think, for as I mentioned earlier, he has done quite a bit on this here, (as part of his thesis work). However, maybe I should wait and see your promised draft (and get on with the missing section, and re-write, of my own). As to main paper, the difficulties of getting our opinions (and protocols) across to each other seems to be substantial, so perhaps we shall have to do them separately; my only objection to this is that its a pity to have two when one could have sufficed, (especially if they come to different conclusions). However, this may be resolved by events. (A day or two of discussion might have done it, but not possible I fear).

I intend to have a bat at the inhibition of trails in 543 by anti-serum for donor's H antigen, transferred to micro-manip. level.

From earlier experiments I am pretty sure it is a genuine effect, seen only (for sure) in 543. Have had some trouble with cross-reactions in sera, so am now in midst of making, and cross-absorbing, some of my own for a change.

An unexpected thing we also mean to look into is trails from TM 2 in presence of anti-i and anti-1,2 after treatment with a particular lysate of a donor which is b-e, nx. As you know it does not normally happen, but we have had quite definite trails on several

occasions, so must now try and find what is the relevant variable.

My T 1 mutants are not going well, too many phenomena but none of any obvious general interest. Marjorie Krauss, from N.Y.U., will, if all goes well, spend some time here in summer. We are thinking of looking for abortive transformations (a propos capsule) in Pn.

I have consulted Race about Proc.Roy.Soc.B. No difficulty in getting in, he says, but variable delay, 6 months or more.

As to terminology, I wonder if we really need to coin a new word ? Jennings after all got by without one. I talked to Sonneborne when he was here a week or two back (he gave 3 excellent lectures) who thought "uni-linear transmission" was O.K., but not "u-l inheritance", since the latter in biology is too much associated with the idea of things which are replicated. A good point I think, He was I found prepared to be convinced by my pedigrees (but of course I had not any of your ? discrepant data to present). Paper to Genetical Soc. went over quite well, discussion at end showed that at least some of audience followed the paper O.K. Pollock (no geneticist he) pointed out resemblance of my "non-replicating gene" to his penicillin-sensitive site or what not, since, if one considers whole culture, each determines linear synthesis of something, pen-ase or m.c.p., during subsequent exponential growth.

Yours sincerely,

Sorry this is so long. I am taking a few days off, going down to Bath for Easter, on my return will try diluted gel-agar with in the way you are doing (Q. has been using it for testing for production of "leeps" where as you know effect is v. striking!. One may I think is that degree of stiffness of standard medium is not always the same, I don't know why. (even after excluding effect of drying etc). I also had no luck with one or two kinds other than Difco. (One lot seemed to destroy gelling power of the agar, even).
Regards to Esther.

P.S. Rumour about trip to Israel was from Andy, who attributed to Science attaché of Israeli Embassy. I will disillusion him when I next see him.